

In addition, as will be apparent from the patentability argument set forth below in connection with the prior art rejections, the use of "a substantially amorphous form" of a substance (substrate of the claimed process) instead of using any other form is an essential feature of the instant invention, and at the same time distinguishes the invention from the cited prior art. A definition of "substantially amorphous" can be found in the second paragraph of page 3 of the instant specification, and how to obtain a "substantially amorphous" form as the substrate for the process is described in the penultimate paragraph of page 7. To use "**substantially** amorphous" and not to use only "amorphous" is proper, as the presence of minor amounts of crystalline (metastable) phases might be possible according to the second paragraph on page 3 of the specification.

Also in connection with the rejection of the claims under 35 U.S.C. §112, the Examiner takes the position that the claims are still considered broad and indefinite with respect to the terminology "organic compounds".

In this regard, the instant claims are directed to a process for the detection of polymorphic forms of **organic compounds** as substrate, characterized in that as substrate the (substantially) **amorphous form** of an organic compound is used. In other words, compounds can be used where different energy forms of one compound are obtainable, thus, anyone compound which is obtainable in different modifications or crystalline forms (polymorphs). Thus, it is proper to limit the scope of potential substrates to compounds of carbon (organic compounds) as those are able to form different modifications due to the characteristic(s) of carbon.

Further, Applicants note that the cited prior art is also concerned with certain processes that are "precise" with regard to the respective "substrate" for those processes. For example, in WO 01/51919, directed to a method, the substrate is "defined" in claim 1 as a "single compound-of-interest"; in claim 8 it is "a pharmaceutical"; and claim 9 "defines" the substrate as "a small molecule". As a further example, in WO 02/052919, directed to a method, the substrate is "defined" in claim 1 as "forms of a sample", and in claim 3 as "one compound".

In view of these considerations, Applicants respectfully submit that one of ordinary skill in the art would be able to determine the scope of the present claims, meaning they are not indefinite, nor are the claims too broad. Accordingly, Applicants respectfully submit that the rejection of the claims under 35 U.S.C. §112 should be withdrawn.

The patentability of the presently claimed invention over the disclosures of the references relied upon by the Examiner in rejecting the claims will be apparent upon consideration of the following remarks.

Thus, the rejection of claims 1-10 under 35 U.S.C. §102(b) or 35 U.S.C. §103(a) based on WO 03/026797, WO 01/51919, WO 02/052919 and the Hilfiker et al. reference is respectfully traversed.

The following comments will also include a discussion of WO 00/60345 which, although not included in the statement of the rejection on page 3 of the Office Action, is discussed by the Examiner on page 4.

The present invention is directed to a process for the detection of polymorphic forms of organic substances, characterized in that as substrate a substantially **amorphous form** thereof is used. The **amorphous form** is generally the form with the **highest free energy** and thus, **with the least thermodynamic stability**. This form is used in parallel studies to search for crystalline forms of lower energy, i.e. to search for thermodynamically more stable forms.

In summary, the instant application teaches an improved process for crystalline form screening. The use of an amorphous form presents a special advantage over the use of any form that is just available. It teaches that in some cases it is advantageous to prepare an amorphous form, then perform screening with the amorphous solid. The specification points out that it makes a difference whether a solution of a small molecule is made from a crystalline or from an amorphous substance, because it presents the advantage of achieving higher concentrations when amorphous materials are used. This is not taught or suggested in any of the references as discussed below.

WO 00/060345: Does not mention the use of an amorphous form as starting material for screening methods.

WO 01/51919: This patent application refers to high-throughput formation, identification and analysis of solid forms. In summary, the document states that "anything can be used". Many pages of this document seem to be copied from chemistry text book(s). However, it does not teach or suggest that exploitation of the amorphous state is an improvement or an advantage.

WO 02/052919: This patent application deals with a screening method for solid form that is specifically designed to be carried out in capillaries. It is a method to produce "high

energy" forms, i.e., less stable forms. It does mention the amorphous form, however, it does not teach or suggest that the amorphous form can be used as mentioned above.

WO 03/026797: Does not mention the use of an amorphous form as starting material for screening methods.

Hilfiker et al. disclose a high-throughput polymorphism screening method using as example carbamazepine as starting material, a substance known to be in a crystalline form as usually available from commercial sources and as taught by the Merck Index. Please note that Hilfiker et al. explicitly use the "**thermodynamically stable form**" of Carbamazepine form III (page 433, line 5 from bottom) and thus, clearly teach away from the instant invention.

The Experimental Section of the present specification provides a comparison test using the known **thermodynamically most stable form** of sertraline HCL, whereby 11 different solid forms were found, however not the known solid form II (last paragraph on page 13). The inventive use of an **amorphous form** of sertraline HCL leads to either 25 found solid forms, including form II (Example 1, page 14) or 16 found solid forms (Example 2, pages 14-15).


In summary, the cited prior art does not anticipate or suggest the instant invention, in that it either is silent about using the substantially amorphous (and therefore thermodynamically least stable) form of a substance (substrate), or explicitly teaches the use of the thermodynamically stable form (Hilfiker et al.). The references fail to motivate the skilled person to use the substantially amorphous form of a compound (substrate) and consequently do not render the instant process obvious.

For these reasons, Applicants take the position that the presently claimed invention is clearly patentable over the applied references.

Therefore, in view of the foregoing remarks, it is submitted that each of the grounds of rejection set forth by the Examiner has been overcome, and that the application is in condition for allowance. Such allowance is solicited.

Respectfully submitted,

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